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(54) **Alkanolamine derivatives and platelet aggregation inhibitors containing the same as an active ingredient.**

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Description

Background of the Invention

1. Field of the Invention

The present invention relates to novel alkanolamine derivatives and platelet aggregation inhibitors containing the same as the active ingredient. Alkanolamines provided by the invention are novel compounds which possess potent platelet aggregation-inhibiting activities. Therefore, they are effective for preventing diseases caused by aggregation of the platelets, that is, such diseases as thrombosis. Also, as it is known that aggregation of the platelets participates in the metastasis of cancers, compounds of the invention are expected to have preventive effects on the cancer metastasis.

2. Description of the Prior Art

α-Linolenic acid which is a trienic higher fatty acid is an essential fatty acid. It is also known that γ-linolenic acid is converted in the living body to dibromo-γ-linolenic acid which is a precursor of prostaglandin E_1. In these respects, both of them are important compounds. Among pentaenic higher fatty acids are reported 5,8,11,14,17-eicosapentaenic acid and 7,10,13,16,19-docosapentaenic acid to be contained in fish oils in a large amount and to possess low-density lipoprotein (LDL)-lowering activities. 5,8,11,14,17-Eicosapentaenic acid is known to have an antithrombocytic activity, which is, however, weak so that development of drugs with improved effects has been desired. There is also strong need for antithrombocytic agents which will effectively prevent thrombosis such as myocardial infarction and cerebral thrombosis, one of the major adult diseases.

DE—A—24 61 798 discloses certain alkyl-phosphoryl-amines that are useful for the treatment of hypertension. There is nothing said about any activity as platelet aggregation inhibitors at all.

The compound disclosed in CA 65 18550 p differs in the position of the double bonds of the octadecatrienoyl group. The citation considers the 9,11,13-octatrienoyl group while the present claims are directed to the 6,9,12- and 9,12,15-position. Furthermore, there is no teaching of any pharmaceutical activity whatsoever.

The compounds cited in FR—A1—2 392 008 and FR—A2—2 346 010 are comparable with the present compounds in having a nicotinic residue. The other groups are, however, different from each other. Namely, the R_3-radical of the cited compounds is a residue of an aromatic acid or a saturated lower alkanoyl acid, whereas that of the present compounds is a residue of an unsaturated higher fatty acid. There is, furthermore, nothing said about a platelet inhibiting activity.

JP—A—56 77259 discloses one single compound, namely N-pyridoxyl-5,8—11,14,17-eicosapentaenoic acid amide which has some activity on the blood platelet coagulation.

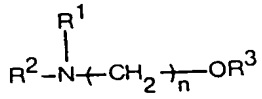
Summary of the Invention

As a result of studies on sythesis of alkanolamine derivatives and pharmacological activities thereof, we have found that they have excellent platelet aggregation-inhibitory activities. The present invention has been completed on the basis of the findings.

It is an object of this invention to provide novel alkanolamine derivatives and platelet aggregation inhibitors containing the same as an active ingredient. The alkanolamines of the invention possess potent platelet aggregation inhibitory activities and are useful for preventing diseases caused by aggregation of the platelets such as thrombosis and cancer metastasis.

Detailed Description of the Invention

According to the present invention, there are provided alkanolamine derivatives represented by the general formula I



(I)

wherein R^1 represents hydrogen atom or a methyl, ethyl or butyl group, R^2 represents hydrogen atom, or an acyl group derived from nicotinic acid, 5,8,11,14,17-eicosapentaenoic acid or 6,9,12- or 9,12,15-octadecatrienoic acid, R^3 represents hydrogen atom, or an acyl group derived from nicotinic acid, 5,8,11,14,17-eicosapentaenoic acid or 6,9,12- or 9,12,15-octadecatrienoic acid or 3-pyridylmethyl group provided that at least one of R^2 and R^3 is a fatty acid residue and n represents 2 or 3, excluding the compounds in which both R^1 and R^2 are hydrogen atoms.

Further according to the invention, there are provided platelet aggregation inhibitors containing compounds of the above-described general formula I as the active ingredient.

It is preferred that R^2 and R^3 are different in the formula I. By platelet aggregation inhibitors in the present invention are meant pharmaceutical preparations that possess platelet aggregation-inhibitory activities.

The alkanolamine derivatives of the invention are obtained by condensing nicotinic acid, one of the mentioned trienic higher fatty acid, the mentioned pentaenic higher fatty acid or a reactive derivative thereof with the corresponding alkanolamine. The reaction temperature is preferably in the range from −10° to 60°C., and the solvent employed is preferably hexane, methylene chloride, chloroform, 1,2-dichlorethane, acetonitrile, benzene or tetrahydrofuran. As the condensing agent used for the condensation is preferably employed, for example, ethyl chloroformate. As the aforementioned reactive derivative may be mentioned thiazolidinethionamide derivatives of said fatty acids. The alkanolamine derivatives of the invention are also obtained by a condensation reaction of an alcoholic hydroxyl group following the above-described condensation reaction with nicotinic acid, said trienic higher fatty acid or said pentaenic higher fatty acid. The reaction temperature is preferably in the range from 0° to 90°C., and the reaction solvent used is preferably methylene chloride, chloroform, 1,2-dichlorethane, acetonitrile or dioxane. As the condensing agent used for said condensation reaction are mentioned, for example, N,N'-dicyclohexylcarbodiimide and 2-chloro-1-methylpyridinium *p*-toluenesulfonate. Alkanolamine derivatives in which both of R^1 and R^2 are hydrogen atoms are prepared by subjecting a phthalimide derivative of an alkanolamine and a carboxylic acid to condensation reaction using N,N'-dicyclohexylcarbodiimide followed by dephthaloylation with hydrazine hydrate. The alkanolamine derivatives in which R^3 represents 3-pyridylmethyl group is prepared by reacting an amide derivative obtained from nicotinic acid, said trienic higher fatty acid, said pentaenic higher fatty acid or a reactive derivative thereof and a corresponding alkanolamine with 3-chloromethylpyridine in the presence of a base such as sodium hydride in an aprotonic solvent such as benzene or toluene.

The alkanolamine derivatives of the present invention can be used in platelet aggregation inhibitors as the active ingredient or as one of the active ingredients, which would be effective in any disease caused by aggregation of the platelets and are particularly useful for preventing thrombosis and metastasis of the cancer. Daily doses are in the range between about 100 and 1500 mg in adults, divided in one to three doses as needed. The administration may be by any suitable route, and is desirably by oral route. Intravenous administration is also suitable.

The compounds of the invention are formulated either alone or with other active ingredients in combination with carriers or excipients into tablets, powders, capsules or granules. As examples of the carrier or excipient are mentioned calcium carbonate, calcium phosphate, starch, sucrose, lactose, talc or magnesium stearate. The compounds of the invention may also be formulated, in addition to the solid preparations as set forth above, into liquid preparations such as oily suspension and syrup.

The compounds of the invention can be stabilized by inclusion with cyclodextrin.

Examples and Test Examples will be given below to describe the invention in more details, but it is to be understood that the invention is not limited thereby in any way.

Example 1

To a solution of 500 mg of 5,8,11,14,17-eicosapentaenic acid thiazolidinethionamide (1.24 mmol) in tetrahydrofuran (10 ml) was added under argon a solution of 84 mg of 2-ethanolamine (1.38 mmol) in tetrahydrofuran (1.5 ml). After reacted at room temperature for 20 min., 10 ml of 1*N*-aqueous solution of sodium hydroxide was added to the reaction mixture, which was then extracted three times with dichloromethane. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to give 437 mg of the extraction residue. The residue was subjected to silica gel column chromatography and was eluted with 95 : 5 chloroform-methanol There was obtained 356 mg (1.03 mmol) of N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol. Physico-chemical properties of the product are given below.

IR ν_{max}^{KBr} (cm^{-1}): 3530, 3340, 1655, 1595, 1530.

^{1}H—NMr ($CDCl_3$) δ : 0.97 (3H t, J=7.5Hz), 1.53—2.33 (8H), 2.67—2.93 (8H), 3.39 (2H q, J=5Hz), 3.70 (2H t, J=5Hz), 5.39 (10H bt, J=5.5Hz).

mass (m/e): 345 (Molecular ion peak), 327 (Dehydration peak), 276.

Example 2

To a suspension of 600 mg (4.87 mmol) of nicotinic acid in tetrahydrofuran (15 ml) was added 0.68 ml (4.88 mmol) of triethylamine under argon at room temperature, followed by addition of a solution of 556 mg (5.12 mmol) of chloro ethylformate in tetrahydrofuran (1 ml) at −10°C. To the mixture, after reacted at −10°C for 13 min., was added a solution of 313 mg (5.12 mmol) of 2-aminoethanol in a solvent mixture of tetrahydrofuran (2 ml) and water (2 ml) at 0°C, followed by addition of 0.72 ml (5.17 mmol) of triethylamine. The mixture was reacted at 0°C for 1 hour and 20 min., followed by addition of 20 ml of water and extraction with three portions of normal butanol. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. The solvent removed by distillation under reduced pressure to give 949 mg of residue from the extraction, which was subjected to silica gel chromatography. There was obtained from a fraction eluted with 97 : 3 chloroform-methanol 608 mg (3.65 mmol) of N-nicotinoyl-2-aminoethanol.

To a solution of 431 mg (1.43 mmol) of 5,8,11,14,17-eiconsapentaenic acid in 1,2-dichlorethane (8 ml) were added solutions of 18 mg (0.15 mmol) of 4-dimethylaminopyridine, 324 mg (1.57 mmol) of N,N'-dicyclohexylcarbodiimide and subsequently 237 mg (1.43 mmol) of N-nicotinoyl-2-aminoethanol

respectively dissolved in N,N-dimethylformamide (4 ml) under argon at room temperature. The mixture was reacted at room temperature for 20 hours, and precipitates thus formed were separated by filtration and washed with benzene. To the mother liquor was added water, and the mixture was extracted with three portions of dichloromethane. The organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to give 665 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained from fractions eluted with 99 : 1 chloroform-methanol 418 mg (0.93 mmol) of N-nicotinoyl-2-aminoethyl 5,8,11,14,17-eicosapentaenoate. Physicochemical properties of the product are given below.

IR ν_{max}^{neat} (cm^{-1}): 3305, 1745, 1655, 1595, 1540.
^1H—NMR ($CDCl_3$) δ: 0.94 (3H t, J=7.5Hz), 1.53—2.43 (8H), 2.67—2.93 (8H), 3.72 (2H q, J=5.5Hz), 4.30 (2H t, J=5.5Hz), 5.37 (10H bt, J=5.5Hz), 7.37 (1H dd, J=8Hz, 5Hz), 8.10 (1H dt, J=8Hz, 2Hz), 8.72 (1H dd, J=5Hz, 2Hz), 8.99 (1H bd, J=2Hz).
mass (m/e): 450 (Molecular ion peak), 381, 149, 106, 78.

Example 3

To a solution of 402 mg (1.44 mmol) of α-linolenic acid in 1,2-dichlorethane (8 ml) were added solutions of 18 mg (0.15 mmol) of 4-dimethylaminopyridine, 328 mg (1.59 mmol) of N,N'-dicyclohexylcarbodiimide and subsequently 240 mg (1.44 mmol) of N-nicotinoyl-2-aminoethanol respectively dissolved in N,N-dimethylformamide (4 ml) under argon at room temperature. The mixture was reacted at room temperature for 14 hours, and precipitates thus formed were separated by filtration and washed with benzene. To the mother liquor was added water, and the mixture was extracted with three portions of dichloromethane. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to give 684 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained from a fraction eluted with 99 : 1 chloroform-methanol 407 mg (0.95 mmol) of N-nicotinoyl-2-aminoethyl 9,12,15-octadecatrienoate. Physicochemical properties of the product are given below.

IR ν_{max}^{neat} (cm^{-1}): 3320, 1750, 1655, 1595, 1545.
^1H—NMR ($CDCl_3$) δ : 0.97 (3H t, J=7Hz), 1.13—2.50 (16H), 2.78 (2H bt, J=5.5Hz), 3.73 (2H q, J=5.5Hz), 4.32 (2H t, J=5.5Hz), 5.33 (6H bt, J=5.5Hz), 7.33 (1H dd, J=8Hz), 8.10 (1H dt, J=8Hz, 2Hz), 8.70 (1H dd, J=5Hz, 2Hz), 8.97 (1H bd, J=2Hz).
mass (m/e): 426 (Molecular ion peak), 357, 149, 106, 78.

Example 4

The same procedures as in Example 3 were carried out using 254 mg (0.912 mmol) of γ-linolenic acid to obtain 280 mg of N-nicotinoyl-2-aminoethyl 6,9,12-octadecatrienoate. Physicochemical data of the product are given below.

IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1740, 1680, 1590, 1520.
mass (m/e): 426 (Molecular ion peak), 149, 106.

Example 5.

To a solution of 77 mg (0.63 mmol) of nicotinic acid in a mixed solvent of tetrahydrofuran (2 ml) and 1,2-dichlorethane (2 ml) were added under argon at room temperature successively solutions of 7 mg (0.06 mmol) of 4-dimethylaminopyridine, 129 mg (0.63 mmol) of N,N'-dicyclohexylcarbodiimide and 196 mg (0.57 mmol) of N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol respectively dissolved in 1,2-dichlorethane (1.5 ml). The mixture was reacted overnight at room temperature, and precipitates thus formed were separated by filtration and washed with benzene. To the mother liquor was added water, and the mixture was extracted with three portions of dichloromethane. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to give 311 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained from a fraction eluted with 98 : 2 chloroform-methanol 246 mg (0.55 mmol) of N-5,8,11,14,17-eicosapentaenoyl-2-aminoethyl nicotinate. Physicochemical data of the product are given below.

IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3425, 1725, 1665, 1580, 1495.
^1H—NMR ($CDCl_3$) δ : 0.93 (3H t, J=7.5Hz), 1.50—2.33 (8H), 2.67—2.93 (8H), 3.67 (2H q, J=5.5Hz), 4.43 (2H t, J=5.5Hz), 5.36 (10H bt, J=5.5Hz), 7.36 (1H dd, J=8Hz, 5Hz), 8.28 (1H dt, J=8Hz, 2Hz), 8.77 (1H dd, J=5Hz, 2Hz), 9.18 (1H bd, J=2Hz).
max (m/e): 450 (Molecular ion peak), 381, 106, 78.

Example 6

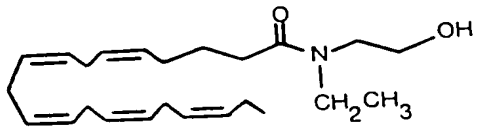
To a solution of 605 mg of 5,8,11,14,17-eicosapentaenic acid in 6 ml of dry chloroform was added 0.25 ml of oxalyl chloride under argon at room temperature. The mixture was reacted for 2 hours. From the

reaction mixture were removed the chloroform and the remaining oxalyl chloride by distillation under reduced pressure to give 5,8,11,14,17-eicosapentaenoyl chloride, which was then dissolved in 6 ml of dry chloroform.

Separately, in a solution of 1.78 g of N-ethyl-ethanolamine in 10 ml of dry chloroform was suspended 553 mg of anhydrous potassium carbonate. To the resulting suspension was added the chloroform solution of 5,8,11,14,17-eicosapentaenoyl chloride prepared above dropwise over 15 min., and the mixture was reacted for 2 hours. From the reaction mixture was removed insolubles by filtration, and water was added to the mother liquor. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 757 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 662 mg of N-ethyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol from a fraction eluted with 98 : 2 chloroform-methanol. Physicochemical data of the product support the structure III given below.

IR ν_{max}^{neat} (cm^{-1}): 3400, 1625

^1H—NMR ($CDCl_3$) δ (ppm): 0.97 (3H t, J=7.5Hz), 1.17 (3H t, J=7.5Hz), 2.60—3.00 (8H), 3.17—3.83 (6H), 5.05—5.76 (10H).



(III)

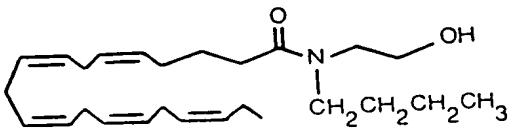
Example 7

To a solution of 1.82 g of 5,8,11,14,17-eicosapentaenic acid in 30 ml of dry chloroform was added 0.80 ml of oxalyl chloride under argon at room temperature. The mixture was reacted for 2 hours. From the reaction mixture was removed the chloroform and the removing oxalyl chloride by distillation under reduced pressure to give 5,8,11,14,17-eicosapentaenoyl chloride, which was then dissolved in 20 ml of dry chloroform.

Separately, in a solution of 7.03 g of N-butylethanolamine in 30 ml of dry chloroform was suspended 1.66 g of anhydrous potassium carbonate. To the suspension was added the chloroform solution of 5,8,11,14,17-eicosapentaenoyl chloride prepared above dropwise over 25 min., followed by reaction for 2 hours. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 2.52 g of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 2.17 g of N-butyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol from a fraction eluted with 98 : 2 chloroform-methanol. Physicochemical data of the product support the structure IV given below.

IR ν_{max}^{neat} (cm^{-1}): 3400, 1620

^1H—NMR ($CDCl_3$) δ (ppm): 0.77—1.10 (6H), 2.60—2.93 (8H), 3.17—3.90 (6H), 5.10—5.60 (10H).



(IV)

Example 8

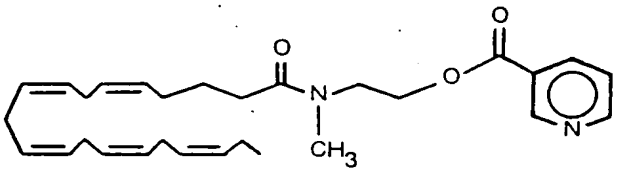
To a solution of 2.40 g of 5,8,11,14,17-eicosapentaenic acid in 15 ml of dry chloroform was added 1.04 ml of oxalyl chloride under argon at room temperature. The mixture was reacted for 2 hours. From the reaction mixture were removed the chloroform and the remaining oxalyl chloride by distillation under reduced pressue to give 5,8,11,14,17-eicosapentaenoyl chloride, which was then dissolved in 15 ml of dry chloroform.

Separately, in a solution of 5.96 g of N-methyl-ethanolamine in 15 ml of dry chloroform was suspended 2.19 g of anhydrous potassium carbonate. To the suspension was added the chloroform solution of 5,8,11,14,17-eicosapentaenoyl chloride prepared above dropwise over 35 min., followed by reaction for 1 hour 30 min. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium

sulfate. Then, the solvent was removed by distillation under reduced pressure to give 2.94 g of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 2.16 g of N-methyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol from a fraction eluted with 98 : 2 chloroform-methanol. To a solution of 2.10 g of the amide-alcohol product in 20 ml of dry benzene at room temperature were added 1.30 g of nicotinoyl chloride hydrochloride and then 3.23 g of anhydrous potassium carbonate, followed by reaction overnight. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor, followed by neutralization with 1*N*-aqueous solution of lithium hydroxide. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and then twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 3.12 g of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 2.05 g of N-methyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethylnicotinate from fractions eluted with chloroform to 98 : 2 chloroform-methanol. Physicochemical data of the product support the structure V given below.

IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1730, 1655, 1595.

^1H—NMR ($CDCl_3$) δ (ppm): 0.97 (3H t, J=7.5Hz), 2.63—2.97 (8H), 3.75 (2H t, J=5.5Hz), 4.50 (2H t, J=5.5Hz), 5.10—5.60 (10H), 7.33 (1H dd, J=8Hz, 5Hz), 8.23 (1H dt, J=8Hz, 2Hz), 8.73 (1H dd, J=5Hz, 2Hz), 9.17 (1H bd, J=2Hz).



(V)

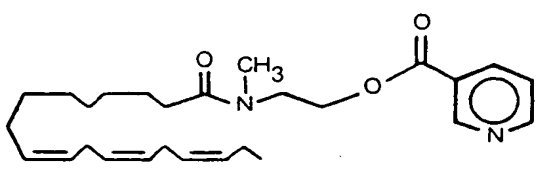
Example 9

To a solution of 834 mg of 9,12,15-octadecatrienoic acid in 8 ml of dry chloroform was added 0.4 ml of oxalyl chloride under argon at room temperature. The mixture was reacted for 2 hours. From the reaction mixture were removed the chloroform and the remaining oxalyl chloride by distillation under reduced pressure to give 9,12,15-octadecatrienoyl chloride, which was then dissolved in 6 ml of dry chloroform.

Separately, in a solution of 2.24 g of N-methylethanol in 4 ml of dry chloroform was suspended 828 mg of anhydrous potassium carbonate. To the suspension was added the chloroform solution of 9,12,15-octadecaatrienoyl chloride prepared above dropwise over 10 min., followed by reaction for 1 hour. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 1.07 g of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 967 mg of N-methyl-N-9,12,15-octadecatrienoyl-2-aminoethanol from a fraction eluted with 98 : 2 chloroform-methanol. To a solution of 943 mg of the amide-alcohol product in 10 ml of dry benzene were added 626 mg of nicotinoyl chloride hydrochloride and then 1.56 g of anhydrous potassium carbonate, followed by reaction overnight. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor, followed by neutralization with 1*N*-aqueous solution of lithium hydroxide. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 1.19 g of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 962 mg of N-methyl-N-9,12,15-octadecatrienoyl-2-aminoethylnicotinate from fractions eluted with chloroform to 98 : 2 chloroform-methanol. Physicochemical data of the product support the structure VI given below.

IR $\bar{\nu}_{max}^{neat}$ (cm^{-1}): 1725, 1650, 1590.

^1H—NMR ($CDCl_3$) δ (ppm): 0.97 (3H t, J=7Hz), 2.80 (4H bt, J=5Hz), 3.57—3.90 (2H), 4.46 (2H t, J=6Hz), 5.00—5.70 (6H), 7.33 (1H dd, J=8Hz, 5Hz), 8.23 (1H dt, J=8Hz, 2Hz), 9.03 (1H dd, J=5Hz, 2Hz), 9.10 (1H bd, J=2Hz).



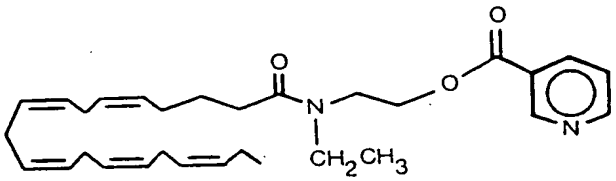
(VI)

Example 10

To a solution of 473 mg of N-ethyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol in 10 ml of dry benzene were added 303 mg of nicotinoyl chloride hydrochloride and then 75 mg of anhydrous potassium carbonate under argon at room temperature. The mixture was reacted overnight. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor, followed by neutralization with 1*N*-aqueous solution of lithium hydroxide. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 761 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 510 mg of N-ethyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethylnicotinate from fractions eluted with 1 : 1 benzene-chloroform to chloroform. Physicochemical data of the product support the structure VII given below.

IR ν_{max}^{neat} (cm^{-1}): 1730, 1650, 1595.

^1H—NMR ($CDCl_3$) δ (ppm): 0.97 (3H t, J=7.5Hz), 1.20 (3H t, J=7.5Hz), 2.58—2.98 (8H), 3.42 (2H q, J=7.5Hz), 3.70 (2H t, J=6Hz), 4.48 (2H t, J=6Hz), 5.05—5.58 (10H), 7.33 (1H dd, J=8Hz, 5Hz), 8.22 (1H dt, J=8Hz, 2Hz), 8.72 (1H dd, J=5Hz, 2Hz), 9.18 (1H bd, J=2Hz).



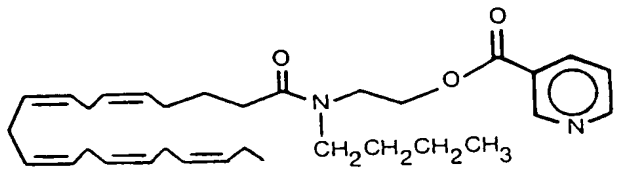
(VII)

Example 11

To a solution of 1.70 g of N-butyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol in 40 ml of dry benzene under argon at room temperature were added 942 mg of nicotinoyl chloride hydrochloride and then 2.40 g of anhydrous pottasium carbonate. The mixture was reacted overnight. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor, followed by neutralization with 1*N*-aqueous solution of lithium hydroxide. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 2.14 g of residue from the extraction. The residue was subjected to silica gel chromatography. There was obtained 2.27 g of N-butyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethylnicotinate from fractions eluted with 1 : 1 benzene-chloroform to chloroform. Physicochemical data of the product support the structure VIII given below.

IR ν_{max}^{neat} (cm^{-1}): 1725, 16.50, 1595.

^1H—NMR ($CDCl_3$) δ (ppm): 0.77—1.12(6H), 2.67—2.97 (8H), 3.78 (2H t, J=5.5Hz), 4.57 (2H t, J=5.5Hz), 5.12—5.70 (10H), 7.33 (1H dd, J=8Hz, 5Hz), 8.23 (1H dt, J=8Hz, 2Hz), 8.73 (1H dd, J=5Hz, 2Hz), 9.15 (1H bd, J=2Hz).



(VIII)

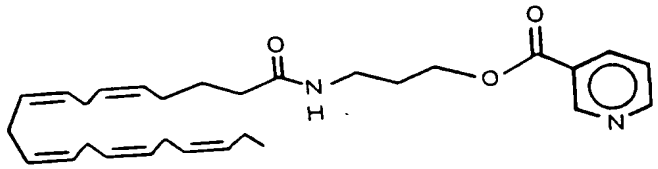
Example 12

To a solution of 302 mg of 5,8,11,14,17-eicosapentaenic acid in 3 ml of dry chloroform was added 0.13 ml of oxalyl chloride under argon at room temperature. The mixture was reacted for 2 hours. From the reaction mixture were removed the chloroform and the remaining oxalyl chloride by distillation under reduced pressure to give 5,8,11,14,17-eicosapentaenic acid chloride, which was then dissolved in 5 ml of dry chloroform.

Separately, in a solution of 753 mg of 3-amino-1-propanol in 5 ml of dry chloroform was suspended under argon 276 mg of anhydrous potassium carbonate. To the suspension was dropwise added the chloroform solution of 5,8,11,14,17-eicosapentaenoyl chloride prepared above at room temperature over 10 min. The mixture was reacted for 2 hours. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor. The mixture was extracted once with a mixed solvent

of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distilation under reduced pressure to give 367 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 243 mg of N-5,8,11,14,17-eicosapentaenoyl-3-aminopropanol from a fraction eluted with 98 : 2 chloroform-methanol. To a solution of the amide-alcohol product in 5 ml of dry benzene at room temperature were added 132 mg of nicotinoyl chloride hydrochloride and then 327 mg of anhydrous potassium carbonate. The mixture was reacted overnight. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor, followed by neutralization with 1*N*-aqueous solution of lithium hydroxide. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 311 mg of residue from the extraction. The residue was subjected silica gel column chromatography. There was obtained 226 mg of N-5,8,11,14,17-eicosapentaenoyl-3-aminopropylnicotinate from a fraction eluted with 98 : 2 chloroform-methanol. Physicochemical data of the product support the structure IX given below.

IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3450, 1725, 1665, 1595, 1515.
^1H—NMR ($CDCl_3$) δ (ppm): 0.97 (3H t, J=7.5Hz), 2.67—2.97 (8H), 3.38 (2H q, J=6Hz), 4.40 (2H t, J=6Hz), 5.10—5.58 (10H), 7.28 (1H dd, J=8Hz, 5Hz), 8.23 (1H dt, J=8Hz, 2Hz), 8.70 (1H dd, J=5Hz, 2Hz), 9.13 (1H bd, J=2Hz).



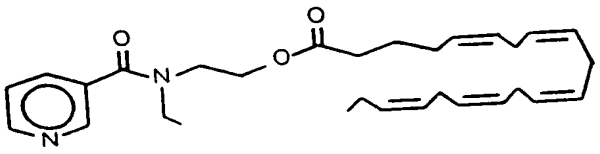
(IX)

Example 13

To a solution of 2.68 g of N-ethylethanolamine in 20 ml of dry chloroform under argon at room temperature were added 3.35 g of anhydrous potassium carbonate and 1.08 g of nicotinoyl chloride hydrochloride successively. The mixture was reacted for 30 min. From the reaction mixture were removed insolubles by filtration, and the mother liquor was concentrated to give 1.72 g of residue. The residue was subjected to alumina column chromatography. There was obtained 989 mg of N-ethyl-N-nicotinoyl-2-aminoethanol from a fraction eluted with chloroform.

Separately, to a solution of 605 mg of 5,8,11,14,17-eicosapentaenic acid in 10 ml of dry chloroform was added 0.26 ml of oxalyl chloride under argon at room temperature. The mixture was reacted for 2 hours. From the reaction mixture were removed the chloroform and the remaining oxalyl chloride to give 5,8,11,14,17-eicosapentaenoyl chloride, which was then dissolved in 6 ml of dry chloroform. The solution thus obtained was added to a solution of 200 mg of N-ethyl-N-nicotinoylethanolamine in 10 ml of dry chloroform under argon at room temperature, followed by reaction overnight. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor, followed by neutralization with 1*N*-aqueous solution of lithium hydroxide. The mixture was extracted once with a mixed solvent of 2 : 1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 942 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 621 mg of (N-ethyl-N-nicotinoyl-2-aminoethyl)-5,8,11,14,17-eicosapentaenoate from fractions eluted with chloroform to 98 : 2 chloroform-methanol. Physicochemical data of the product support the structure X given below.

IR ν_{max}^{neat} (cm^{-1}): 1740, 1645, 1595.
^1H—NMR ($CDCl_3$) δ (ppm): 0.97 (3H t, J=7.5Hz), 1.17 (3H t, J=6Hz), 2.61—2.98 (8H), 3.42 (2H q, J=6Hz), 3.65 (2H t, J=6Hz), 4.28 (2H t, J=6Hz), 5.08—5.65 (10H), 7.27 (1H dd, J=8Hz, 5Hz), 7.68 (1H dt, J=8Hz, 2Hz), 8.53—8.72 (2H).



(X)

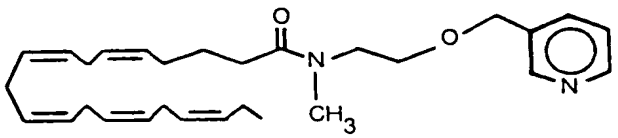
Example 14

To a solution of 595 mg of N-methyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol in 12 ml of dry benzene was added under argon 299 mg of β-picolyl chloride hydrochloride. To the resulting mixture

cooled in a water bath to 6°C was added 147 mg of 60% oily sodium hydride. The mixture was reacted at 6°C for 2 hours, at room temperature for 16 hours and with heating under reflux for 2 hours. Additional 33 mg of 60% oily sodium hydride was then added, and heating under reflux was continued for additional 30 min. The reaction mixture after allowed to cool was diluted with dichloromethane to double the volume, followed by addition of ice water. The mixture was neutralized under ice cooling with 1*N*-hydrochloric acid and extracted three times with dichloromethane. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 612 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 461 mg of [N-methyl-N-(5,8,11,14,17-eicosapentaenoyl)-2-aminoethyl]-β-picolylether from a fraction eluted with 99 : 1 chloroform-methanol. Physicochemical data of the product support the structure XI given below.

IR ν_{max}^{neat} (cm^{-1}): 1650.

^1H—NMR ($CDCl_3$) δ (ppm): 0.97 (3H t, J=7.5Hz), 2.67—3.07 (11H), 3.43—3.70 (4H), 4.50 (2H, s), 5.03—5.60 (10H), 7.23 (1H dd, J=8Hz, 5Hz), 7.60 (1H dt, J=8Hz, 2Hz), 8.40—8.58 (2H).

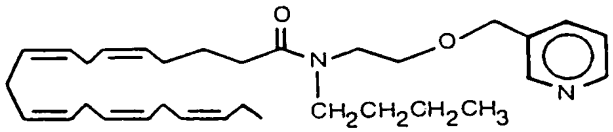


(XI)

Example 15

To a solution of 848 mg of N-butyl-N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol in 17 ml of dry benzene was added under argon 382 mg of β-picolyl chloride hydrochloride. To the resulting mixture was added at room temperature 228 mg of 60% oily sodium hydride, followed by reaction with heating under reflux for 1 hour 30 min. The reaction mixture after allowed to cool was diluted with dichloromethane to double the volume, followed by addition of ice water. The mixture was neutralized under ice cooling with 1*N*-hydrochloric acid and then extracted three times with dichloromethane. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 883 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 585 mg of [N-butyl-N-(5,8,11,14,17-eicosapentaenoyl)-2-aminoethyl β-picolyl ether from a fraction eluted with chloroform. IR absorption spectrographic data of the product XII are given below.

IR ν_{max}^{neat} (cm^{-1}): 1650, 1110.



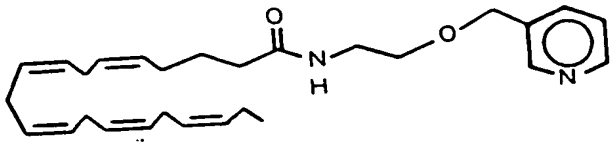
(XII)

Example 16

To a solution of 691 mg of N-5,8,11,14,17-eicosapentaenoyl-2-aminoethanol in 15 ml of dry benzene was added under argon 394 mg of β-picolyl chloride hydrochloride. To the mixture at room temperature was added 264 mg of 60% oily sodium hydride, followed by reaction with heating under reflux for 1 hour 20 min. The reaction mixture after allowed to cool was diluted with dichloromethane to double the volume, followed by addition of ice water. The mixture was neutralized under ice cooling with 1*N*-hydrochloric acid and then extracted three times with dichloromethane. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure to give 982 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 553 mg of (N-5,8,11,14,17-eicosapentaenoyl)-2-aminoethyl β-picolyl ether from a fraction eluted with 99:1 chloroform-methanol. Physiochemical data of the product support the structure XIII given below.

IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3450, 1665, 1515.

^1H-NMR ($CDCl_3$) δ(ppm): 0.97 (3H t, J=7.5Hz), 2.60—3.07 (8H), 3.37—3.67 (4H), 4.50 (2H s), 5.03—5.60 (10H), 7.23 (1H dd, J=8Hz, 5Hz), 8.20 (1H dt, J=8Hz, 2Hz), 8.40—8.58 (2H).



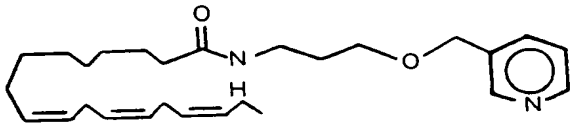
(XIII)

Example 17

To a solution of 834 mg of 9,12,15-octadecatrienic acid in 8 ml of dry chloroform was added 0.4 ml of oxalyl chloride under argon at room temperature. The mixture was reacted for 2 hours. From the reaction mixture were removed the chloroform and the remaining oxalyl chloride by distillation under reduced pressure to give 9,12,15-octadecatrienoyl chloride, which was then dissolved in 6 ml of dry chloroform.

Separately, in a solution of 2.25 g of 3-amino-1-propanol in 5 ml of dry chloroform was suspended under argon 830 mg of anhydrous potassium carbonate. To the suspension was added the chloroform solution of 9,12,15-octadecatrienoyl chloride prepared above dropwise at room temperature over 10 min., followed by reaction for 1 hour. From the reaction mixture were removed insolubles by filtration, and water was added to the mother liquor. The mixture was extracted once with a mixed solvent of 2:1 chloroform-ether and twice with chloroform. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solution was removed by distillation under reduced pressure to give 1.09 g of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 970 mg of N-9,12,15-octadecatrienoyl-3-amino-1-propanol from a fraction eluted with 98:2 chloroform-methanol. To 576 mg of the amide alcohol product dissolved in 15 ml of dry benzene was added 340 mg of picolyl chloride hydrochloride. To the mixture was added 227 mg of 60% oily sodium hydride at room temperature. The resulting mixture was reacted with heating under reflux for 1 hour 30 min. The reaction mixture after allowed to cool was diluted with dichloromethane to double the volume, followed by addition of ice water. The mixture was neutralized under ice cooling with 1*N*-hydrochloric acid and then extracted three times with dichloromethane. Organic layer of the extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was removed under reduced pressure to give 903 mg of residue from the extraction. The residue was subjected to silica gel column chromatography. There was obtained 515 mg of (N-9,12,15-octadecatrienoyl)-3-aminopropyl β-picolylether from a fraction eluted with 99:1 chloroform-methanol. IR absorption spectroscopic data of the product XIV is given below.

IR$\nu_{max}^{CHCl_3}$ (cm^{-1}): 3450, 1665, 1515.



(XIV)

Preparation Example 1: Capsule

(Formulation)

Active drug:	N-methyl-N-5,8,11,14,17-eicosapentaenoyl-2-amino-ethylnicotinate	200 mg
Excipient:	Corn starch	196.5 mg
Lubricant:	Magnesium stearate	3.5 mg
	Total (per capsule)	400 mg

To the active drug, N-methyl-N-5,8,11,14,17-eicosapentaenyl-2-aminoethylnicotinate is added the excipient. The mixture, either in powder or in granule, is mixed with the lubricant to a uniform blend, which is filled in hard capsules.

Preparation Example 2: Tablet

(Formulation)			
Active drug:	N-5,8,11,14,17-eicosa-pentaenoyl-3-aminopropyl nicotinate	500	mg
Excipient:	Crystalline cellulose	67	mg
" :	Corn starch	89	mg
" :	Lactose	44	mg
Disintegrator:	Calcium carboxymethyl-cellulose	25	mg
Binder:	Hydroxypropylcellulose	62.5	mg
Lubricant:	Magnesium stearate	12.5	mg
	Total (per tablet)	800	mg

The active drug, N-5,8,11,14,17-eicosapentaenoyl-3-aminopropyl nicotinate are mixed with the excipients, the disintegrator and the binder to a uniform blend. The blend is granulated, and the granules are mixed with the lubricant. The mixture is formed under compression into tablets. As needed, the tablets thus obtained may be coated with an appropriate coating agent (for example, hydroxypropylmethyl-cellulose or shellac).

Test Example

Platelet Aggregation-Inhibitory Action

Blood was drawn from the carotid artery of a rabbit using a syringe containing 3.8% solution of sodium citrate in an amount of a volumes per volume of the solution. The blood was centrifuged to obtain platelet-rich plasma (PRP: 5×10^5 platelets/µl).

In a cuvette was placed 250 µl of the PRP, which is warmed in a constant-temperature bath at 37°C for 2 min. To the warmed cuvette was added 20 µl of a solution of an alkanolamine derivative to be tested (a 7×10^3 *M* ethanol solution which had been diluted with Tris-buffered isotonic saline solution). The mixture was then incubated for 3 min., followed by addition of a aggregation inducer, an arachidonic acid solution or a collagen solution. Measurement of the platelet aggregation was made by Born's turbidometric method (e.g., described in J. Physiol., Vol. 168, P. 178, 1968). The 50% inhibitory concentration for the platelet aggregation caused by arachidonic acid (100 µ*M*) or collagen (20 µg/ml) is given in Table 1 with reference to Aspirin for comparison.

As shown in Table 1, the typical compounds tested were found to possess marked platelet aggregation inhibitory activities. It was also confirmed that alkanolamine derivatives according to the present invention other than those shown in Table 1 possessed similar anti-aggregation activities. The 50% inhibitory concentration as shown in the table means the concentration of an alkanolamine derivative required for inhibiting aggregation ability of the platelets to 50% when the aggregation ability of the platelets in the absence of the alkanolamine derivative of the invention is taken as 100%.

Table 1. Platelet aggregation inhibitory activity

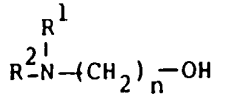
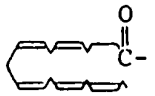
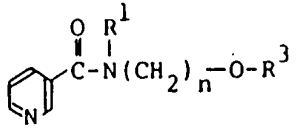
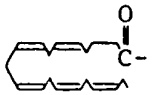
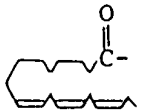
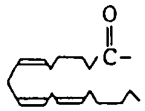
Structure	Example No.	R^1	R^2 or R^3	n	50% inhibitory concentration (mole)	
					Arachidonic acid	Collagen
	1	H		2	2.2×10^{-5}	9.8×10^{-5}
	2	H		2	1.1×10^{-5}	9.3×10^{-5}
	3	H		2	4.9×10^{-5}	1.4×10^{-4}
	4	H		2	3.6×10^{-5}	1.9×10^{-4}

Table 1. (Continued)

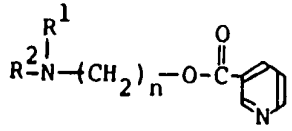
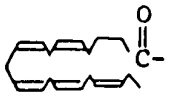
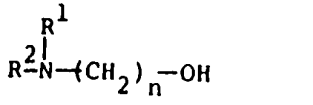
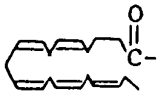
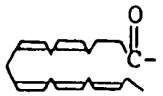
Structure	Example No.	R^1	R^2 or R^3	n	50% inhibitory concentration (mole)	
					Arachidonic acid	Collagen
	5	H		2	8.8×10^{-6}	9.0×10^{-5}
	6	Et		2	3.57×10^{-6}	2.73×10^{-4}
	7	Bu		2	3.55×10^{-6}	1.87×10^{-4}

Table 1 (Continued)

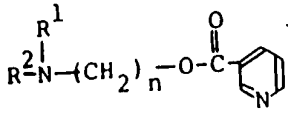
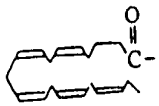
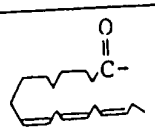
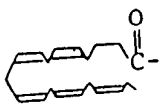
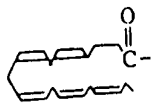
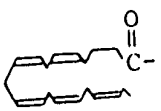
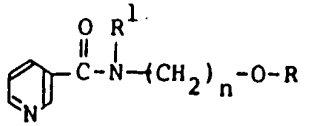
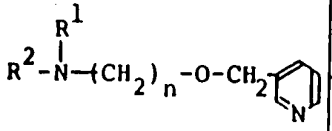
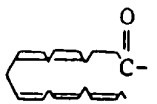
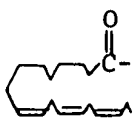
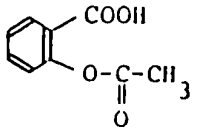
Structure	Example No.	R^1	R^2 or R^3	n	50% inhibitory concentration (mole)	
					Arachidonic acid	Collagen
	8	Me		2	6.62×10^{-6}	1.11×10^{-4}
	9				8.24×10^{-6}	2.73×10^{-4}
	10	Et		2	4.99×10^{-6}	9.17×10^{-5}
	11	Bu		2	6.03×10^{-6}	1.97×10^{-4}
	12	H		3	3.44×10^{-6}	5.53×10^{-5}

Table 1. (Continued)

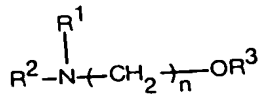
Structure	Example No.	R^1	R^2 or R^3	n	50% inhibitory concentration (mole)	
					Arachidonic acid	Collagen
	13	Et		2	2.55×10^{-4}	4.01×10^{-4}
	14	Me		2	5.68×10^{-6}	5.01×10^{-5}
	15	Bu		2	7.07×10^{-6}	1.23×10^{-4}
	16	H		2	5.68×10^{-6}	5.01×10^{-5}
	17	H		2	7.07×10^{-6}	1.23×10^{-4}
	for comparison	-	———	-	1.40×10^{-5}	1.36×10^{-5}

Acute Toxicity

Acute toxicity test was conducted by oral administration using ICR male mice (4 weeks old). LD_{50} values are 500 mg/kg bodyweight or high for any of the compounds of the invention, thereby demonstrating high safety.

Claims

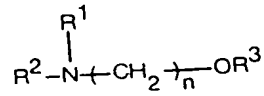
1. Alkanolamine derivatives represented by the general formula I



(I)

wherein R^1 represents hydrogen atom or a methyl, ethyl or butyl group, R^2 represents hydrogen atom, or an acyl group derived from nicotinic acid, 5,8,11,14,17-eicosapentaenoic acid or 6,9,12- or 9,12,15-octadecatrienoic acid, R^3 represents hydrogen atom, or an acyl group derived from nicotinic acid, 5,8,11,14,17-eicosapentaenoic acid or 6,9,12- or 9,12,15-octadecatrienoic acid or 3-pyridylmethyl group provided that at least one of R^2 and R^3 is a fatty acid residue and n represents 2 or 3, excluding the compounds in which both R^1 and R^2 are hydrogen atoms.

2. Platelet aggregation inhibitors containing a medicinally effective amount of an active ingredient of an alkanolamine derivative represented by the general formula I

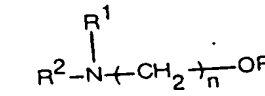


(I)

wherein R^1 represents hydrogen atom or a methyl, ethyl or butyl group, R^2 represents hydrogen atom, or an acyl group derived from nicotinic acid, 5,8,11,14,17-eicosapentaenoic acid or 6,9,12- or 9,12,15-octadecatrienoic acid, R^3 represents hydrogen atom, or an acyl group derived from nicotinic acid, 5,8,11,14,17-eicosapentaenoic acid or 6,9,12- or 9,12,15-octadecatrienoic acid or 3-pyridylmethyl group provided that at least one of R^2 and R^3 is a fatty acid residue and n represents 2 or 3, excluding the compounds in which both R^1 and R^2 are hydrogen atoms, and a pharmaceutical carrier therefor.

Patentansprüche

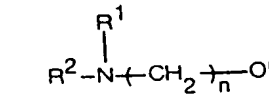
1. Alkanolaminderivate der allgemeinen Formel:



(I)

worin bedeuten: R^1 ein Wasserstoffatom oder eine Methyl-, Ethyl- oder Butylgruppe; R^2 ein Wasserstoffatom oder eine von Nikotinsäure, 5,8,11,14,17-Eicosapentaen- oder 6,9,12- oder 9,12,15-Octadecatriensäure abgeleitete Acylgruppe; R^3 ein Wasserstoffatom oder eine von Nikotin-, 5,8,11,14,17-Eicosapentaen- oder 6,9,12- oder 9,12,15-Octadecatriensäure abgeleitete Acylgruppe oder eine 3-Pyridylmethylgruppe, wobei gilt, daß mindestens einer der Reste R^2 und R^3 für einen Fettsäurerest steht, und n = 2 oder 3, mit der Ausnahme der Verbindungen, in denen beide Reste R^1 und R^2 Wasserstoffatome darstellen.

2. Plättchenaggregationsinhibitoren mit einer medizinisch wirksamen Menge eines aktiven Bestandteils in Form eines Alkanolaminderivats der allgemeinen Formel:



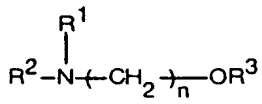
(I)

worin bedeuten: R^1 ein Wasserstoffatom oder eine Methyl-, Ethyl- oder Butylgruppe; R^2 ein Wasserstoffatom oder eine von Nikotinsäure, 5,8,11,14,17-Eicosapentaen- oder 6,9,12- oder 9,12,15-

Octadecatriensäure abgeleitete Acylgruppe; R^3 ein Wasserstoffatom oder eine von Nikotin-, 5,8,11,14,17-Eicosapentaen- oder 6,9,12- oder 9,12,15-Octadecatriensäure abgeleitete Acylgruppe oder eine 3-Pyridylmethylgruppe, wobei gilt, daß mindestens einer der Reste R^2 und R^3 für einen Fettsäurerest steht, und n = 2 oder 3, mit der Ausnahme der Verbindungen, in denen beide Reste R^1 und R^2 Wasserstoffatome darstellen, und einem pharmazeutischen Träger hierfür.

Revendications

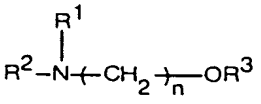
1. Dérivés d'alcanolamines représentés par la formule générale I



(I)

dans laquelle R^1 représente un atome d'hydrogène ou un radical méthyle, éthyle ou butyle, R^2 représente un atome d'hydrogène ou un radical acyle dérivé de l'acide nicotinique, de l'acide 5,8,11,14,17-eicosapentaénoïque ou de l'acide 6,9,12- ou 9,12,15-octadécatriénoïque, R^3 représente un atome d'hydrogène ou un groupe acyle dérivé de l'acide nicotinique, de l'acide 5,8,11,14,17-eicosapentaénoïque ou de l'acide 6,9,12- un 9,12,15-octadécatriénoïque ou un groupe 3-pyridylméthyle, sous réserve qu'au moins un de R^2 et R^3 soit un reste d'acide gras et n représente 2 ou 3, à l'exclusion des composés dans lesquels R^1 et R^2 sont tous deux des atomes d'hydrogène.

2. Inhibiteurs de l'agrégation des plaquettes contenant une quantité médicinale efficace d'un ingrédient actif constitué d'un dérivé d'alcanolamine représenté par la formule générale I



(I)

dans laquelle R^1 représente un atome d'hydrogène ou un radical méthyle, éthyle ou butyle, R^2 représente un atome d'hydrogène ou un radical acyle dérivé de l'acide nicotinique, de l'cide 5,8,11,14,17-eicosapentaénoïque ou de l'acide 6,9,12- ou 9,12,15-octadécatriénoïque, R^3 représente un atome d'hydrogène ou un groupe acyle dérivé de l'acide nicotinique, de l'acide 5,8,11,14,17-eicosapentaénoïque ou de l'acide 6,9,12- un 9,12,15-octadécatriénoïque ou un groupe 3-pyridylméthyle, sous réserve qu'au moins un de R^2 et R^3 soit un reste d'acide gras et n représente 2 ou 3, à l'exclusion des composés dans lesquels R^1 et R^2 sont tous deux des atomes d'hydrogène, et un véhicule pharmaceutique de celui-ci.